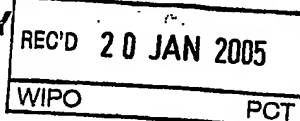


PATENT COOPERATION TREATY



From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/002493

International filing date (day/month/year)
11.06.2004

Priority date (day/month/year)
12.06.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/138, A61K45/06, A61K31/55, A61K31/343

Applicant
THE WWK TRUST

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. 1 Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial
applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1,2,8,10 (partially); 3-5,7,9,11-13,15-23

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1,2,8,10 (partially); 3-5,7,9,11-13,15-23
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

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Box No. IV... Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1,2,6,8,10,14 (partially)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	-
	No: Claims	1,2,6,8,10,14
Inventive step (IS)	Yes: Claims	-
	No: Claims	1,2,6,8,10,14
Industrial applicability (IA)	Yes: Claims	1,2,6,8,10,14
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
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Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43*bis*.1 and 70.9)
see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Present claims 1,2,8,10 encompass a genus of compounds defined only by their function (precursor or inducer of a neurotransmitter other than L-tryptophan), wherein the relationship between the structural features of the members of the genus and said function has not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore, no complete search has been performed for claims 1,2,8,10 (Articles 5,6 PCT). The search has been restricted to the explicitly defined compounds of claim 6 for the treatment of depression. No Written Opinion of the International Search Authority will be carried out in respect of subject-matter which is not covered by the search report (Rule 66(1)(e) PCT).

Re Item IV.

2.1 The separate inventions/groups of inventions are:

1,2,6,8,10,14 (partially)

Use for treating depression of a composition comprising "C",
wherein:

C is a precursor or inducer of a neurotransmitter, in particular L- phenylalanine, L-tyrosine, tyramine.

1-5,8-13,16-20,23 (partially)

Use for treating depression of a composition comprising A and B,
wherein:

A is an antidepressant, in particular lofepramine, fluoxetine, citalopram, paroxetine;
B is vitamin B12.

1-4,6,8-12,14,16-19,21,23 (partially)

Use for treating depression of a composition comprising A and C,

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wherein:

A is an antidepressant, in particular lofepramine, fluoxetine, citalopram, paroxetine;

C is a precursor or inducer of a neurotransmitter, in particular L-phenylalanine, L-tyrosine, tyramine.

1-4,8-11,16-19,23 (partially), 7,15,22

Use for treating depression of a composition comprising A and C',

wherein:

A is an antidepressant, in particular lofepramine, fluoxetine, citalopram, paroxetine;

C' is L-tryptophan.

1,2,5,6,8-10,13,14,16,17,20,21,23 (partially)

Use for treating depression of a composition comprising B and C, or C',

wherein:

B is vitamin B12;

C is a precursor or inducer of a neurotransmitter, in particular L-phenylalanine, L-tyrosine, tyramine;

C' is L-tryptophan.

1-6,8-14,16-21,23 (partially)

Use for treating depression of a composition comprising A, B and C, or C',

wherein:

A is an antidepressant, in particular lofepramine, fluoxetine, citalopram, paroxetine;

B is vitamin B12;

C is a precursor or inducer of a neurotransmitter, in particular L-phenylalanine, L-tyrosine, tyramine;

C' is L-tryptophan.

2.2 They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons. The problem to be solved by the present invention is to provide a medicament for treating depression. The proposed solution is to use a compositions comprising:

C,

A and B

A and C, or C'

B and C, or C'

A, B and C, or C'

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wherein:

A is an antidepressant, in particular lofepramine, fluoxetine, citalopram, paroxetine;

B is vitamin B12;

C is a precursor or inducer of a neurotransmitter, in particular L-phenylalanine, L-tyrosine, tyramine;

C' is L-tryptophan

The use of the above mentioned compositions in the treatment of depression represents the technical feature common to these (structurally) different compounds and to the different compositions claimed.

The document US6200607 cited in the search report discloses that tyrosine, one of the three claimed compounds defined as C, is useful for treating depression, together with an iron containing compound (see claims 1,2,3): iron is, according to D1, also a precursor of a neurotransmitter, dopamine.

The document WO0185165 discloses that S-adenosyl methionine is useful for treating depression. S-adenosyl methionine is a well known neurotransmitter inducer, involved in the methylation of the neurotransmitters.

Consequently, because a precursor or inducer of a neurotransmitter, as claimed, has already been used in the treatment of depression, the activity as antidepressants can no longer serve as a single general inventive concept linking the compounds and the compositions claimed, which have no other technical feature in common.

Moreover, the use of antidepressants (A) together with precursors of neurotransmitters is also already known in the art: see US6096317, where S-adenosyl methionine, inducer involved in the biosynthesis of neurotransmitters, is administered together with St. John's wort, well known antidepressant and mood enhancer.

Therefore the uses of the compositions above mentioned, "A and C" and "A and C'" in the treatment of depression represent each a distinct invention, characterised by its own special technical features, i.e. the structural features of the compounds.

The documents cited above do not represent a comprehensive search for the defined inventions and are to be considered in the present context only as part of the prior art pertaining to the general idea underlying the present application.

Re Item IV.

3. The following documents are referred to in this communication:

D1: US 6 200 607 B1 (BRIDGEMAN KEITH) 13 March 2001 (2001-03-13)

D2: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE,

- COLUMBUS, OHIO, US; SENSBA, JUNICHI ET AL: "Evaluation of antidepressant properties of monoamine precursors by the forced-swimming test in mice" XP002297603 retrieved from STN Database accession no. 1988:563333
- D3: US 6 096 317 A (DESANTIS DEBBIE A ET AL) 1 August 2000 (2000-08-01)
- D4: WO 01/85165 A (ECKERT GUENTHER P ; HASSELWANDER OLIVER (DE); BASF AG (DE); KRAEMER KL) 15 November 2001 (2001-11-15)
- D5: BECKMANN H ET AL: "DL-PHENYLALANINE IN DEPRESSED PATIENTS: AN OPEN STUDY" JOURNAL OF NEURAL TRANSMISSION, SPRINGER VERLAG, VIENNA, AT, vol. 41, 1977, pages 123-134, XP000612721 ISSN: 0300-9564
- D6: EP 1 112 693 A (QUEST INT) 4 July 2001 (2001-07-04)
- D7: DATABASE WPI Section Ch, Week 200252 Derwent Publications Ltd., London, GB; Class B05, AN 2002-482614 & JP 2002 078463 A (BIOENERGENE CO LTD) 19 March 2002 (2002-03-19)
- D8: PICKAR D ET AL: "TYRAMINE INFUSIONS IN BI POLAR ILLNESS BEHAVIORAL EFFECTS AND LONGITUDINAL CHANGES IN PRESSOR SENSITIVITY" AMERICAN JOURNAL OF PSYCHIATRY, vol. 136, no. 11, 1979, pages 1460-1463, XP008035917 ISSN: 0002-953X

Novelty

4.1 D1 discloses compositions comprising a tyrosine compound and an iron containing compound for treating depression. D2 seems to mention that tyrosine has an antidepressant activity (according to the abstract: the original is in Japanese).

Phenylalanine is also already known in the art for treating depression: D5 discloses the use of phenylalanine against depression, and trials thereof. D8 discloses that tyramine induces an alteration in mood and cognition and on the behaviour in the patients.

The subject-matter of claims 1,2,6,8,10,14 is therefore not new in the sense of Article 33(2) PCT.

4.2 D3 discloses S-adenosyl methionine, which is a neurotransmitter precursor, involved in the synthesis of MAO and dopamine through methylation processes, as being useful for treating depression and anxiety. D4 discloses compositions containing the inducer of neurotransmitters S-adenosyl methionine together with lipoic acid, for treating depression. S-adenosyl methionine falls under the definition of "C", according to claim 1, being an inducer of neurotransmitters.

The subject-matter of claims 1,2,8,10 is therefore not new in the sense of Article 33(2) PCT.

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4.3 Concerning claims 8,10,14, the attention of the applicant is drawn to the fact that these claims, as they are formulated, relate to a process for the preparation of a composition containing the claimed compounds, where the only technical feature is the step of admixing the components. Any document disclosing the preparation of a pharmaceutical composition containing phenylalanine, tyramine or tyrosine will be novelty destroying for such claims. D6 and D7 disclose such compositions and their preparation.

The subject-matter of claims 8,10,14 is therefore not new over D6, D7 in the sense of Article 33(2) PCT.

Inventive step

5. The subject matter of present claims 1,2,6,8,10,14, is not novel and therefore does not meet the requirements of Article 33(3) PCT, because it does not involve an inventive step.